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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,133	02/09/2001	Neil J. Hayward	PPI-064	1688

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EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	PAPER NUMBER
1654	9

DATE MAILED: 11/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/781,133	Applicant(s) HAYWARD ET AL.	
	Examiner Jeffrey E. Russel	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *1-23,33-46 and 48-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-32 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election without traverse of the invention of Group II, claims 24-32 and 47, in Paper No. 8 is acknowledged.

Claims 1-23, 33-46, and 48-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Applicant's election without traverse of the species PPI-1019 in Paper No. 8 is acknowledged.

2. The Sequence Listing filed February 9, 2001 is approved.

3. The disclosure is objected to because of the following informalities: At page 3, line 27, "cholinesterase" is misspelled. Appropriate correction is required.

4. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. At claim 25, line 2, "or" should be changed to "and" so that standard Markush language is used.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24-32 and 47 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 7, and 15-17 of copending Application No. 09/519,019 in view of the WO Patent Application 98/08868, Kroin et al (U.S. Patent No. 5,776,939), and the WO Patent Application 95/20980. The '019 application claims the PPI-1019 β-amyloid peptide derivative and pharmaceutical compositions for delivering PPI-1019 across the blood-brain barrier. However, the '019 application does not claim a method for administering PPI-1019 across the blood-brain barrier, does not claim oral administration of the PPI-1019, and does not claim co-administration of a P-glycoprotein inhibitor or a cytochrome P450 inhibitor in order to improve the oral administration or in order to increase the crossing of the blood-brain barrier. The WO Patent Application '868 teaches β-amyloid peptide derivatives which are structurally and functionally analogous to the PPI-1019 β-amyloid peptide derivative claimed by the '019 application (see, e.g., the Abstract and the claims), and teaches the desirability of oral administration of the β-amyloid peptide derivatives (see, e.g., page 33, lines 7-8) and discloses the desirability of administration of the β-amyloid peptide derivatives so that they cross the blood-brain barrier (see, e.g., page 34, line 34 - page 35, line 5). Kroin et al teach co-administration of drugs with a compound of Formula (C) so that the oral bioavailability of the drugs and the bioavailability of the drugs to the brain is enhanced. The compounds of Formula (C) are P-glycoprotein inhibitors. The drugs and the compounds of Formula (C) are administered simultaneously or at different times. See, e.g., column 2, lines 53-60; column 4, lines 4-17; column 9, lines 39-42; column 25, lines 57-64; and column 26, lines 4-6. The WO Patent Application '980 teaches co-administration of an orally administered drug with an inhibitor of a cytochrome P450 3A enzyme and/or an inhibitor of P-glycoprotein-

mediated membrane transport so that the bioavailability of the drug is increased. Cyclosporine, SDZ PSC-833 (i.e. valspodar), antiarrhythmics, antibiotics, antifungals, antiparasites, calcium channel blockers, cancer chemotherapeutics, hormones, local anesthetics, phenothiazines, and tricyclic antidepressants are disclosed as useful inhibitors. The drugs and inhibitors can be administered simultaneously or at different times. See, e.g., the Abstract; page 12, lines 9-17; page 13, line 22 - page 14, line 8; page 18; page 26; and page 32, line 30 - page 33, line 5. It would have been obvious to one of ordinary skill in the art to administer the claimed compound of the '019 application by the same methods disclosed by the WO Patent Application '868 for its β-amyloid peptide derivatives because it is routine in the art to administer a drug by the same methods and for the same purposes as other prior art analogs of the drug have been administered, and because it is prima facie obvious to use a product consistently with the intended use limitation recited in a claim drawn to the product (see claim 17 of the '019 application). It would have been obvious to one of ordinary skill in the art to co-administer the PPI-1019 β-amyloid peptide derivative claimed by the '019 application with the P-glycoprotein inhibitors and/or the cytochrome P450 inhibitors of Kroin et al or the WO Patent Application '980 because the methods of Kroin et al and the WO Patent Application '080 are disclosed to be useful for a wide variety of drugs, and because the methods of Kroin et al and the WO Patent Application '080 would have been expected to be useful in aiding and increasing the oral administration and the crossing of the blood-brain barrier which are suggested to be desirable for PPI-1019 by the WO Patent Application '868.

This is a provisional obviousness-type double patenting rejection.

6. Claims 24-32 and 47 are directed to an invention not patentably distinct from claims 6, 7, and 15-17 of commonly assigned 09/519,019. Specifically, see the above provisional obviousness-type double patenting rejection.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned 09/519,019, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

7. Instant claims 24-32 and 47 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/181,833 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention. Accordingly, the effective filing date of instant claims 24-32 and 47 is deemed to be February 11, 2000.

The effective filing date of instant claims 6, 7, and 15-17 of copending application 09/519,019 is deemed to be March 3, 1999, the filing date of provisional application 60/122,736. Claims 6, 7, and 15-17 of copending application 09/519,019 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/181,833 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention. Accordingly, because the inventorship of copending application 09/519,019 is different than the inventorship of the instant application, and because copending application 09/519,019 has an earlier effective filing date than the instant application, copending application 09/519,019 is provisionally available as prior art against the instant claims under 35 U.S.C. 102(e).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

9. Claims 24-32 and 47 are provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 09/519,019 which has a common assignee with the instant application in view of the WO Patent Application 98/08868, Kroin et al (U.S. Patent No. 5,776,939), and the WO Patent Application 95/20980. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if published or patented. This provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future publication or patenting of the conflicting application. See the above provisional obviousness-type double patenting rejection

This provisional rejection might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application prior to the effective U.S. filing date of the copending application under 37 CFR 1.131. For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the

claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

10. Claims 24, 25, 31, 32, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 98/08868 in view of Applicants' admission at page 11, lines 2-3, of the specification. The WO Patent Application '868 teaches β-amyloid peptide derivatives which are administered in vivo to the CNS or across the BBB for the diagnosis and treatment of amyloidogenic diseases. Administration can be as a single bolus or a several divided doses. Supplementary active compounds can be incorporated into the compositions. Two or more of the β-amyloid peptide derivatives may be used in combination. Particularly exemplified β-amyloid peptide derivatives include PPI-558, PPI-578, PPI-655, and PI-657. See, e.g., page 5, lines 26-32; page 32, lines 22-25; page 33, lines 13-14; page 36, lines 31-32; page 39, line 32 - page 41, line 8; and Tables VIII, X, and XI. With respect to the teachings in the WO Patent Application '868 of the administration of a single β-amyloid peptide derivative, Applicants admit at page 11, lines 2-3, that β-amyloid peptide derivatives are themselves P-glycoprotein inhibitors. Accordingly, the teachings in the WO Patent Application '868 of the administration of a single β-amyloid peptide derivative constitute an inherent teaching of the administration of both a β-amyloid peptide derivative and a P-glycoprotein inhibitor. Note that the claims do not contain any limitations requiring the β-amyloid peptide derivatives and the P-glycoprotein inhibitors to be chemically distinct compounds. It follows then that the WO Patent Application '868's teaching of administering the β-amyloid peptide derivatives either as a single bolus or in several divided doses constitutes an inherent teaching of the simultaneous or non-simultaneous

administration of a β-amyloid peptide derivative and a P-glycoprotein inhibitor. With respect to the teachings in the WO Patent Application '868 of the administration of two or more β-amyloid peptide derivatives in combination, again Applicants admit at page 11, lines 2-3, that β-amyloid peptide derivatives are themselves P-glycoprotein inhibitors. Accordingly, at least one of the β-amyloid peptide derivatives in the WO Patent Application '868's combination can be designated as corresponding to Applicants' β-amyloid peptide derivative, and at least one of the other β-amyloid peptide derivatives in the WO Patent Application '868's combination can be designated as inherently corresponding to Applicants' P-glycoprotein inhibitor.

11. Claims 24, 31, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 98/08868 in view of the WO Patent Application 95/20980. Application of the WO Patent Application '868 is the same as in the above rejection of claims 24, 25, 31, 32, and 47. The WO Patent Application '868 at page 34, lines 30-33, teaches a preferred formulation comprising the β-amyloid peptide derivatives in combination with Tween-80, and at page 36, lines 7-10, teaches the β-amyloid peptide derivatives in combination with liposomes. The WO Patent Application '980 teaches that Tween-80 and liposomes are inherently P-glycoprotein inhibitors (see page 26, column 2). Because the same active agents are being administered by the same method steps in the WO Patent Application '868 and in Applicants' claims, inherently the bioavailability of the β-amyloid peptide derivatives of the WO Patent Application '868 will be enhanced by the Tween-80 and the liposomes of the WO Patent Application '868 to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the methods and compositions of the WO Patent Application '868 and the instant claimed

invention to shift the burden to Applicants to provide evidence that their claimed method and composition are unobviously different than those of the WO Patent Application '868.

12. Claims 24, 25, 27-32, and 47 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 98/08868 as applied against claims 24, 25, 31, 32, and 47 above, and further in view of Kroin et al (U.S. Patent No. 5,776,939) or the WO Patent Application 95/20980. The WO Patent Application '868 discloses the desirability of oral administration of the β-amyloid peptide derivatives (see, e.g., page 33, lines 7-8) and discloses the desirability of administration of the β-amyloid peptide derivatives so that they cross the blood-brain barrier (see, e.g., page 34, line 34 - page 35, line 5), but does not recite co-administration of a P-glycoprotein inhibitor or a cytochrome P450 inhibitor in order to improve the oral administration or in order to increase the crossing of the blood-brain barrier. Kroin et al teach co-administration of drugs with a compound of Formula (C) so that the oral bioavailability of the drugs and the bioavailability of the drugs to the brain is enhanced. The compounds of Formula (C) are P-glycoprotein inhibitors. The drugs and the compounds of Formula (C) are administered simultaneously or at different times. See, e.g., column 2, lines 53-60; column 4, lines 4-17; column 9, lines 39-42; column 25, lines 57-64; and column 26, lines 4-6. The WO Patent Application '980 teaches co-administration of an orally administered drug with an inhibitor of a cytochrome P450 3A enzyme and/or an inhibitor of P-glycoprotein-mediated membrane transport so that the bioavailability of the drug is increased. Cyclosporine, SDZ PSC-833 (i.e. valspodar), antiarrhythmics, antibiotics, antifungals, antiparasites, calcium channel blockers, cancer chemotherapeutics, hormones, local anesthetics, phenothiazines, and tricyclic antidepressants are disclosed as useful inhibitors. The drugs and inhibitors can be administered

simultaneously or at different times. See, e.g., the Abstract; page 12, lines 9-17; page 13, line 22 - page 14, line 8; page 18; page 26; and page 32, line 30 - page 33, line 5. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to co-administer the β-amyloid peptide derivatives of the WO Patent Application '868 with the P-glycoprotein inhibitors and/or the cytochrome P450 inhibitors of Kroin et al or the WO Patent Application '980 because the methods of Kroin et al and the WO Patent Application '080 are disclosed to be useful for a wide variety of drugs, and because the methods of Kroin et al and the WO Patent Application '080 would have been expected to be useful in aiding and increasing the oral administration and the crossing of the blood-brain barrier taught desirable by the WO Patent Application '868.

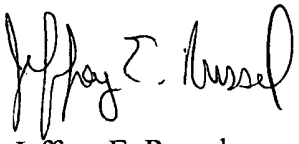
13. Claims 24, 28, 31, and 47 are rejected under 35 U.S.C. 102(a) as being anticipated by the WO Patent Application 99/10374. The WO Patent Application '374 teaches conjugates of an Aβ-binding peptide and a cyclosporin A derivative. The conjugates, in combination with pharmaceutically acceptable carriers, are administered in vivo to treat neurological diseases. See, e.g., the Abstract; page 9, lines 23-30; and page 12, line 24 - page 13, line 2. Because the same active agents are being administered by the same methods steps in the WO Patent Application '374 and in Applicants' claims, inherently the bioavailability of the Aβ-binding peptide of the WO Patent Application '374 will be enhanced by the cyclosporin of the WO Patent Application '374 to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the methods and compositions of the WO Patent Application '374 and the instant claimed invention to shift the burden to Applicants to provide evidence that their

claimed method and composition are unobviously different than those of the WO Patent Application '374.

14. Claims 24, 28, 30, 31, and 47 are rejected under 35 U.S.C. 102(a) as being anticipated by the WO Patent Application 99/10374 as applied against claims above, and further in view of the WO Patent Application 95/20980. The WO Patent Application '980 teaches that the cyclosporin of the WO Patent Application '374 is both a cytochrome P450 inhibitor (see page 18, column 1) and a P-glycoprotein inhibitor (see page 26, column 2).

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

November 7, 2002